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# Observation by NMR of cationic Wheland-like intermediates in the deiodination of protected 1-iodonaphthalene-2,4-diamines in acidic media

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1-Iodonaphthalene-2,4-diamines in trifluoroacetic acid / chloroform give stable Wheland-like tetrahedral cationic species observable by NMR, through an initial intramolecular protonation. Dynamic equilibria allow proton-deuterium exchange of aromatic protons and provide a mechanism for deiodination of 1-iodonaphthalene-2,4-diamines.

## Introduction

Cyclopropabenzindoles (CBI) are more biologically potent, stable and synthetically accessible analogues of cyclopropapyrroloindole (CPI) antitumour antibiotics, such as duocarmycin-SA **1** and CC1065 **2** (Figure 1).<sup>1,2</sup> These compounds are exquisitely potent cytotoxins (**1** shows IC<sub>50</sub> = 10 pM against L1210 cells)<sup>3</sup> but it is this very potency that makes them difficult to develop as selective anticancer drugs. Recently, much effort has gone into developing prodrugs (*e.g.* **3,4**) for selective delivery of CPIs and CBIs to tumours.<sup>2,4</sup> Efficient routes to the required hydroxy-*seco*-CBIs are available but access to the corresponding amino-*seco*-CBIs is more challenging.<sup>5,6</sup>

As part of our research towards a general route to amino-*seco*-CBIs, di-Boc-1-iodonaphthalene-2,4-diamine **11** was prepared from 2,4-dinitronaphthalen-1-ol **6** in five steps, as shown in Scheme 1. Inexpensive Martius Yellow **6** was triflated at oxygen,

forming **7**.<sup>5</sup> S<sub>N</sub>Ar displacement of the triflate with iodide then produced the iodonaphthalene **8** in good yield. Unfortunately, reduction of the nitro groups of **8** was accompanied by complete loss of the iodine to form the naphthalenediamine **9**, which was converted into the di-Boc-protected derivative **10**. The iodine was restored electrophilically with an I<sup>+</sup>-equivalent generated from N-iodosuccinimide and toluenesulfonic acid, affording the key intermediate **11**. For our route, we needed to discriminate between the two amine nitrogens in **11** to access either **12** or **13** or to form the diamine **14** (for later selective reprotection) by treatment with a dilute (0.85%, one equiv.) solution of trifluoroacetic acid in dichloromethane (Scheme 1). However even prolonged reaction (*ca.* 7 days, 20°C) only resulted in the isolation of **10**, from unanticipated loss of iodine but retention of the normally acid-labile Boc groups. Further attempts with more concentrated solutions of CF<sub>3</sub>CO<sub>2</sub>H removed both Boc groups but the iodine was lost, giving **9**. To understand the process more fully, a series of NMR-scale experiments was undertaken, leading to identification of un-

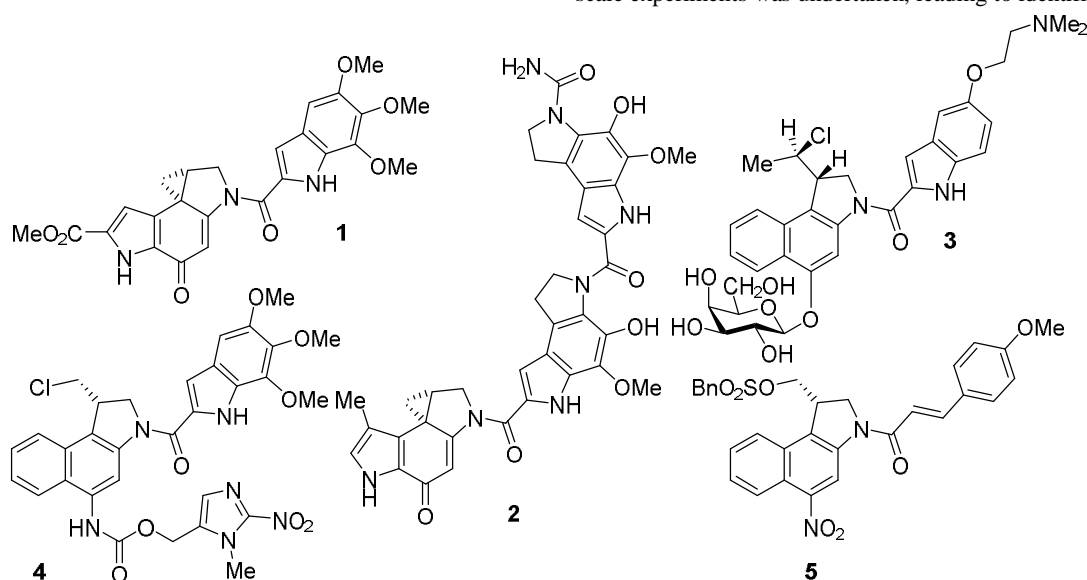
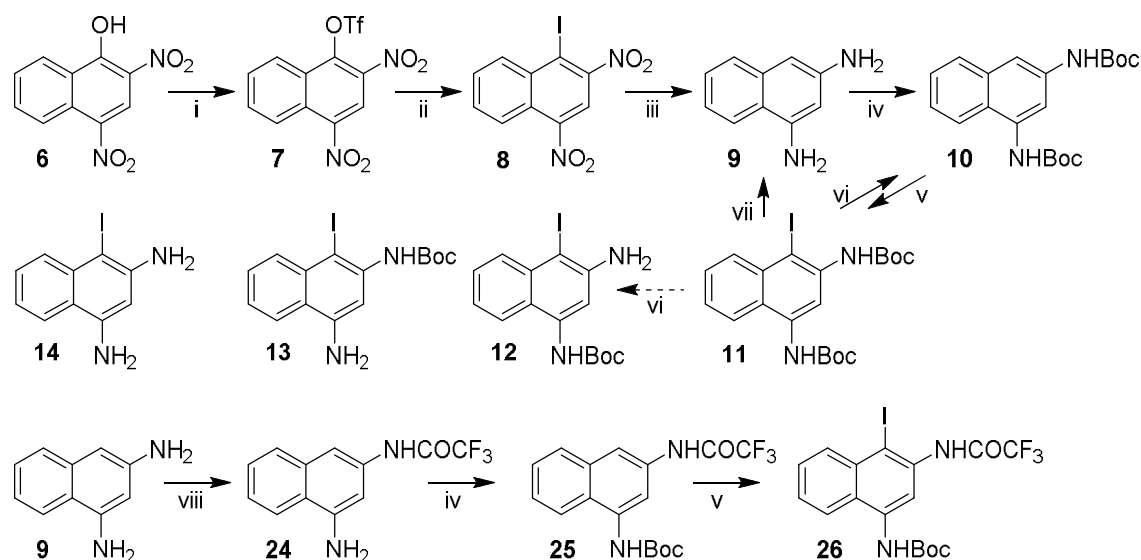


Figure 1. Structures of duocarmycin-SA **1**, CC1065 **2** and representative prodrugs of CBIs **3-5**.



**Scheme 1.** Syntheses of protected 1-iodo-2,4-dinitronaphthalenes **11** and **26** used in the study and reaction of **11** with  $\text{CF}_3\text{CO}_2\text{H}$ . Reagents: i,  $\text{TiF}_4$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; ii,  $\text{NaI}$ , acetone,  $\Delta$ ; iii,  $\text{SnCl}_2$ ,  $\text{EtOAc}$ ; iv,  $\text{Boc}_2\text{O}$ ,  $\text{THF}$ ,  $\Delta$ ; v,  $N$ -iodosuccinimide,  $\text{TsOH}$ ,  $\text{THF}$ ,  $\text{MeOH}$ ; vi, 0.85%  $\text{CF}_3\text{CO}_2\text{H}$  in  $\text{CH}_2\text{Cl}_2$ ; vii, >5%  $\text{CF}_3\text{CO}_2\text{H}$  in  $\text{CH}_2\text{Cl}_2$ ; viii,  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{Pr}^t_2\text{NEt}$ ,  $\text{THF}$ .

expected cationic Wheland-like intermediates.

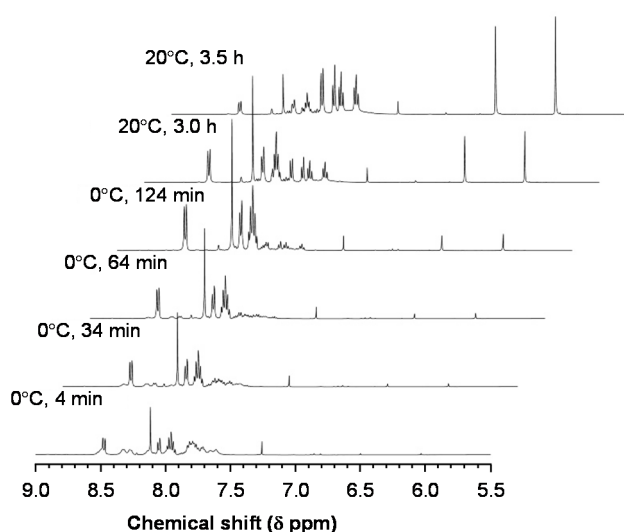
## Results and discussion

Compound **11** was dissolved in deuteriochloroform (150  $\mu\text{L}$ ) and  $\text{CF}_3\text{CO}_2\text{H}$  (450  $\mu\text{L}$ ) at  $0^\circ\text{C}$  in a 5 mm NMR tube and introduced to the pre-cooled spectrometer probe. The course of the reaction was followed by  $^1\text{H}$  NMR at  $0^\circ\text{C}$  for 120 min, during which time both Boc groups were cleaved to give **15** in good yield (>90%, by  $^1\text{H}$  NMR) (Scheme 2). Although the NMR spectrum of **10** is clear, it was noted that new peaks upfield of the signals for the aromatic protons of **15** were slowly appearing. Raising the temperature to  $20^\circ\text{C}$  caused these new signals to become dominant until, after 2 h at  $20^\circ\text{C}$ , they were present at >90%, with loss of the peaks for **15**; selected  $^1\text{H}$  NMR spectra from this experiment are shown in Figure 2. The new compound was fully assigned through 1-D and 2-D NMR experiments and was identified as the Wheland intermediate-like tetrahedral cationic species **16**.<sup>‡</sup> Most significant is the signal at  $\delta$  9.64 in the  $^{13}\text{C}$  spectrum, arising from an  $\text{sp}^3$  carbon, with an associated proton signal at  $\delta$  6.50, as shown by HSQC. The upfield shift of the aromatic proton can be attributed to the loss of aromaticity, the stabilisation of the positive charge in the compound and the shielding effects of the iodine. 3- $\text{H}^\#$  also experiences a significant upfield shift of 2.06 ppm. Cation **16** is relatively stable in  $\text{CF}_3\text{CO}_2\text{H}$  / chloroform solution, with little change during 7 d at  $20^\circ\text{C}$ . However, all attempts at isolation afforded only the de-iodinated product **9**.

More information about the reaction was obtained using  $\text{CF}_3\text{CO}_2\text{D}$ . The overall course of the reaction was similar, with removal of both Boc groups at  $0^\circ\text{C}$  at 2 h and at  $20^\circ\text{C}$ , a tetrahedral cationic species again formed. However, both the signal at  $\delta$  6.50 (1-H) and the signal at  $\delta$  6.05 (3-H) show smaller than expected intensity, as a result of H $\rightarrow$ D exchange. Interestingly, this effect is seen even when only small amounts of **18** have been formed. Initially, the signal for 1-H integrates for 0.24 H (*i.e.* 76% of the 1-H have been replaced with deuterium), whereas 3-H integrates for only 0.10 H. The presence of D at the 1- and 3-

positions was confirmed by the  $^{13}\text{C}$  showing as a triplet owing to  $^{13}\text{C}$ -D coupling. Over time, the intensity of the 1-H signal decreased further; ultimately the ratio of the signals for the aromatic protons to these signals is close to 10:1, which reflects of the overall ratio of exchangeable D to H in solution. The presence of a larger signal for protium at 1-H than for the overall ratio in solution at early time points provides mechanistic information. Addition of a deuteron to 2-N is rapid but H/D exchange at this nitrogen is slow, so that full equilibration of H and D is not complete in the time taken to obtain the first NMR data. It follows that the protonation at the 1-C is likely to be *intramolecular* from the  $\text{N}^+\text{H}_2\text{D}$  or the  $\text{Bu}^t$  cation is the source; if it were *intermolecular* from the trifluoroacetic acid, then the ratio of H/D in the Wheland-like species would reflect the overall solution ratio from the start. Since 3-H displays this ratio at all times, exchange at this position is much more rapid and may proceed directly from solvent. It is likely that the solution contains a mixture of dications and monocations but only the monocations have sufficient electron density to react (thus only the reactive monocations are shown in Scheme 2).

Similar experiments were undertaken with **9**, with  $\text{CF}_3\text{CO}_2\text{H}$  and with  $\text{CF}_3\text{CO}_2\text{D}$  (Scheme 2). Treatment of **9** with  $\text{CF}_3\text{CO}_2\text{H}$  / deuteriochloroform at  $20^\circ\text{C}$  afforded a mixture of two compounds, assigned as the di-protonated naphthalenediamine **20** and a tetrahedral species **21**, in ratio *ca.* 4:1, as shown by NMR. Of particular note is the presence of a  $\text{CH}_2$  in **21**, confirmed by a phase-sensitive HSQC spectrum with a correlation peak at  $\delta$  4.13 in  $^1\text{H}$  and  $\delta$  33.27 in  $^{13}\text{C}$ . As with the iodo-compound **11**, the aromatic protons show a marked up-field shift in moving to the cationic Wheland species. There was little or no change in the ratio **20** : **21** in  $\text{CF}_3\text{CO}_2\text{H}$  during 7 d at  $20^\circ\text{C}$ . When the experiment was repeated with  $\text{CF}_3\text{CO}_2\text{D}$ , deuterium was found to wash into both the 1- and 3-positions of **23** and, significantly, into the 1- and 3-positions of **22**. This provides confirmation that **22** and **23** are in equilibrium. Surprisingly, the initial spectral data for **23** showed that the signal for 1-H integrates to almost two protons



**Figure 2.** Time-course of  $^1\text{H}$  NMR spectra of reaction of **11** with  $\text{CF}_3\text{CO}_2\text{H} / \text{CDCl}_3$  (3:1).

relative to the other aromatic protons and thus has very little deuterium incorporated when first formed. As with the formation of **16** / **18**, this gives strong evidence for an intramolecular mechanism of protonation at 1-C, as the  $\text{Bu}^t$  cation is absent from this reaction mixture. After 48 h, this signal had reduced in size and a new triplet, slightly upfield at  $\delta$  4.14, arose. This peak correlated with a signal for a carbon with one proton attached (from the DEPT135 spectrum) and is assigned as CHD. The signal for 3-H also diminishes rapidly as deuterium was incorporated; at 4 min, the 3-H signal integrated for 0.18 H, whereas 1-H integrated for 1.0 H. Exchange at 3-H is much more rapid than for 1-H. Incorporation of D has a marked effect on the  $^{13}\text{C}$  signals for 1-C and 3-C.

To explore the effect of a non-acid-labile amide group at  $\text{N}^3$ , the  $\text{N}^1$ -Boc- $\text{N}^3$ -TFA differentially protected naphthalenediamine **26** was prepared (Scheme 1). Treatment of **9** with stoichiometric trifluoroacetic anhydride in dilute solution in THF achieved selective protection of the less-hindered amine in 15% yield. Interestingly, Hawkins *et al.*<sup>7</sup> reported selective introduction of Boc at this position with Boc-ON but in only 8% yield of crude material. Masking the remaining amine with Boc and introduction of the iodine gave **26**. With trifluoroacetamide adjacent to the iodine, treatment of **26** with  $\text{CF}_3\text{CO}_2\text{H}$  in deuteriochloroform did not lead to NMR-observable concentrations of any tetrahedral cation. Following loss of Boc, only **27** was observed and, after 48 h, iodine was lost to afford **28**, shown by the presence of a signal at  $\delta$  8.29 for 1-H. Significantly, when  $\text{CF}_3\text{CO}_2\text{D}$  was used, both this peak and 3-H showed a reduced intensity after 48 h, indicating that deuterium is incorporated. A transient Wheland cationic species may be involved but the equilibrium concentration is too low for observation. Deuterium was also incorporated into **29** / **30**.

In each case where Boc was lost, the NMR spectra showed that the  $\text{Bu}^t$  was trapped by solvent as  $\text{Bu}^t$  trifluoroacetate. With  $\text{CF}_3\text{CO}_2\text{D}$ , deuterium was incorporated, giving clearly identifiable  $\text{F}_3\text{CCO}_2\text{C}(\text{CH}_3)(\text{CH}_3)(\text{CH}_2\text{D})$ ,  $\text{F}_3\text{CCO}_2\text{C}(\text{CH}_3)(\text{CH}_2\text{D})-(\text{CH}_2\text{D})$  and  $\text{F}_3\text{CCO}_2\text{C}(\text{CH}_3)(\text{CH}_3)(\text{CHD}_2)$  species, showing that

2-methylpropene is an intermediate.

Electrophilic aromatic substitution proceeds *via* an initial  $\pi$ -complex, which converts to a “ $\sigma$ -complex”; the latter is better recognised as the covalent Wheland intermediate. Several  $\sigma$ -complexes have been identified by their charge-transfer UV-vis absorptions and by crystallography.<sup>8</sup> The vast majority of Wheland intermediates are extremely transient, owing to rapid deprotonation, only being observed by fs time-resolved laser absorption spectroscopy. A few examples have sufficient lifetime to be characterised by NMR. 1,3,5-Trimethylbenzene and hexamethylbenzene react with  $\text{NO}_2^+\text{BF}_4^-$  in super-acid media at  $-70^\circ\text{C}$  to give NMR-observable Wheland intermediates but these decompose on warming.<sup>9</sup> Wheland intermediates have been isolated with carbonyl counter-anions (characterised by NMR at low temperature)<sup>10</sup> and where the molecule contains both Wheland-like cations and Meisenheimer-like anions.<sup>11</sup> The formation of Wheland intermediates from 1,3-tris(dialkylamino)benzenes under acidic conditions has been studied and reviewed by Effenberger.<sup>12</sup> Wheland intermediate cations have also been observed by NMR in azo-coupling reactions of these molecules with arenediazonium salts.<sup>13</sup> UV spectroscopy and thermochemical studies have been reported to show Wheland-like structures from protonation of benzene-1,3,5-triamine.<sup>14</sup>

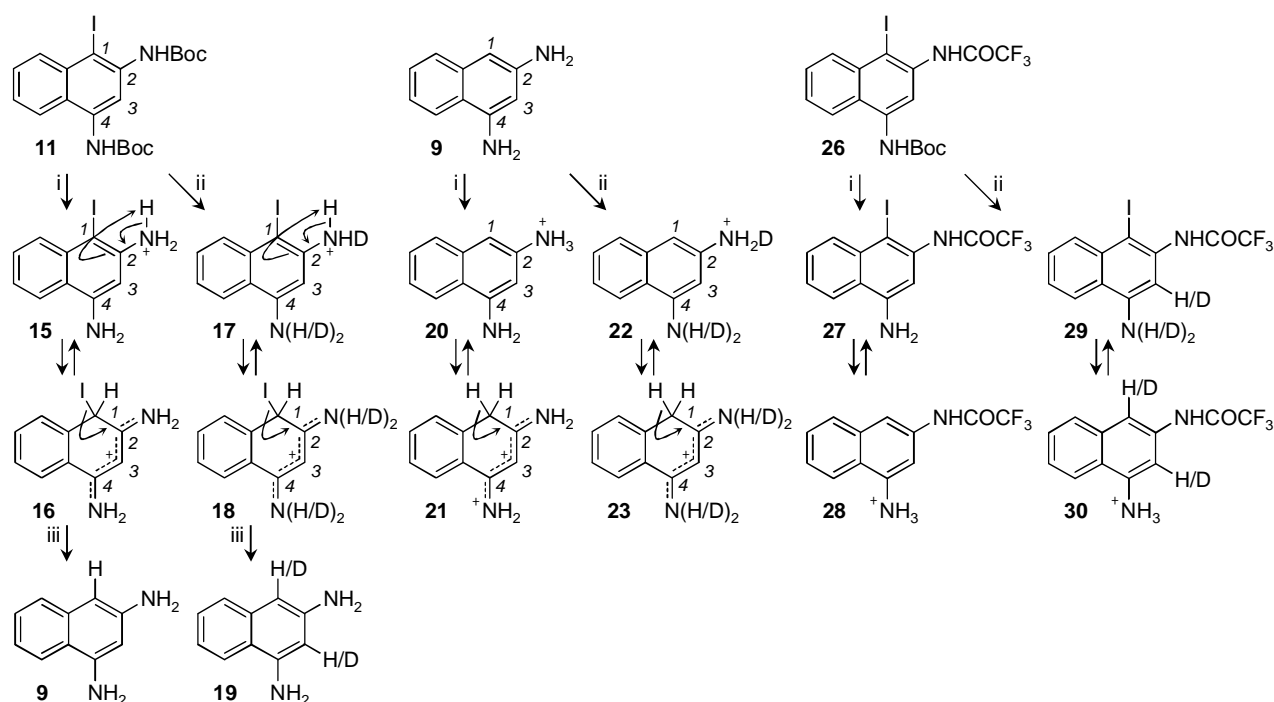
We believe that this is the first direct observation by NMR of Wheland-like intermediates derived from naphthalenes; these cations are remarkably stable, even at room temperature, but decompose on attempted isolation. The formation of these stable carbocationic species provides a partial explanation for the unexpected loss of iodine in attempts to cleave Boc groups from **6**. The iodine must be lost from the cationic species as an electrophilic  $\text{I}^+$ -equivalent. Presumably, the trapping nucleophile is trifluoroacetate, although, at very long time-points ( $>7$  d), the solutions turn dark red, suggesting the presence of  $\text{I}_2$ .

The abundant tetrahedral Wheland-like species **16** / **18**, observed by NMR, is stabilised both by delocalisation of charge (including with the nitrogens) and by relief of steric compression between the very large iodine ( $R = 1.98 \text{ \AA}$ ) and the *peri* 8-H as it moves from the  $\text{sp}^2$ -hybridised educt to the  $\text{sp}^3$ -hybridised 1-C in the cation. However, the presence of iodine in the molecule is not essential for the formation of these cationic species, as shown by the formation of **21** / **23** and the reactions of **27** / **29**. Figure 3 shows space-filling representations of MM2-minimised structures of **15** and **16**, to illustrate this point.

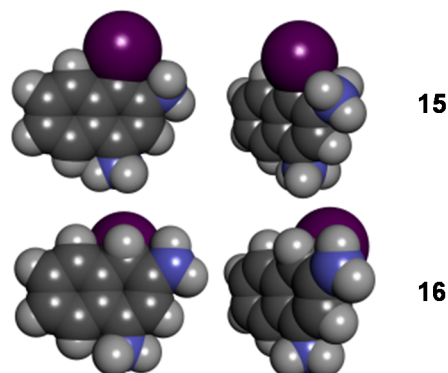
## Conclusions

Here we report the generation of Wheland-like intermediates from (Boc-protected) naphthalenediamines. When the adjacent amine lacks an electron-withdrawing carbonyl, these intermediates are present in high concentrations in trifluoroacetic acid, characterisable by  $^1\text{H}$  and  $^{13}\text{C}$  NMR at  $0^\circ\text{C}$  and at  $20^\circ\text{C}$ , much higher than have been used previously for less-stabilised benzenium cations. Strikingly, the source of the proton at the new tetrahedral carbon is shown to be intramolecular, through a 1,3-proton shift. These studies provide evidence for the mechanism of protio-deiodination of *ortho*-iodoanilines and *ortho*-iodoanilides.

## Experimental



**Scheme 2.** Reactions of **11**, **9** and **26** with  $\text{CF}_3\text{CO}_2\text{H}$  and with  $\text{CF}_3\text{CO}_2\text{D}$  in  $\text{CDCl}_3$ , showing intramolecular 1,3-proton shifts to form Wieland-like intermediates **16**, **18**, **21** and **23** and numbering scheme used throughout. Reagents: i,  $\text{CF}_3\text{CO}_2\text{H}$  /  $\text{CDCl}_3$  (3:1); ii,  $\text{CF}_3\text{CO}_2\text{D}$  /  $\text{CDCl}_3$  (3:1); iii, aq. work-up.



**Figure 3.** Space-filling representations of MM2-minimised structures of **15** and **16**, showing relief of steric crowding on moving to tetrahedral  $\text{sp}^3$  1-C in **16**.

nesium sulfate. All reagents and solvents were of commercial reagent grade and were used without further purification. The brine was saturated.

#### 2,4-Dinitronaphthalen-1-yl trifluoromethanesulfonate (**7**)

Martius Yellow (2,4-dinitronaphthalen-1-ol) **6** (501 mg, 2.14 mmol) and triethylamine (562 mg, 5.6 mmol) in dichloromethane (10 mL) were cooled in an ice bath and treated dropwise with trifluoromethanesulfonic anhydride (784 mg, 2.8 mmol). The mixture was stirred at  $20^\circ\text{C}$  for 2 h under  $\text{N}_2$ . Aq. HCl (0.5 M, 10 mL) was added in one portion and the mixture was stirred for 30 min. The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were washed with sat. aq. sodium hydrogen carbonate and brine. Drying, evaporation and chromatography (dichloromethane) gave **7** (484 mg, 62%) as a yellow solid: mp  $117\text{--}119^\circ\text{C}$  (lit.<sup>5</sup> mp  $105\text{--}107^\circ\text{C}$ );  $\nu_{\text{max}}$  1532 ( $\text{NO}_2$ ), 1365 ( $-\text{SO}_2\text{O}-$ ), 1349 ( $\text{NO}_2$ );  $\delta_{\text{H}}$  ( $(\text{CD}_3)_2\text{SO}$ ) 7.72 (1 H, ddd,  $J$  8.2, 7.1, 1.0 Hz, 7-H), 7.91 (1 H, ddd,  $J$  8.4, 7.0, 1.4 Hz, 6-H), 8.51 (1 H, d,  $J$  8.4 Hz, 8-H), 8.57 (1 H, d,  $J$  8.6 Hz, 5-H), 8.87 (1 H, s, 3-H);  $\delta_{\text{C}}$  ( $(\text{CD}_3)_2\text{SO}$ ) 120.65 (q,  $J$  322.3 Hz,  $\text{CF}_3$ ), 122.31 (3-C), 123.32 (5-C), 125.58 (8-C), 127.49 (2-C), 127.76 (8a-C, 7-C), 128.00 (4a-C), 133.09 (6-C), 134.75 (4-C), 158.70 (1-C);  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -71.85 (s,  $\text{CF}_3$ ).

#### 1-Iodo-2,4-dinitronaphthalene (**8**)

Compound **7** (4.28 g, 11.7 mmol) was heated under reflux with sodium iodide (5.99 g, 40 mmol) in acetone (170 mL) for 2 h. The evaporation residue, in ethyl acetate, was washed with sat. aq. sodium thiosulfate and dried. Evaporation and chromatogra-

phy (dichloromethane) gave **8** (2.98 g, 74%) as a yellow solid: mp 183–186°C (lit.<sup>5</sup> mp 194–195°C);  $\nu_{\max}$  1530 (NO<sub>2</sub>), 1333 (NO<sub>2</sub>);  $\delta_{\text{H}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) 7.98 (2 H, m, 6,7-H<sub>2</sub>), 8.32 (1 H, dd, *J* 7.1, 1.7 Hz, 5-H), 8.52 (1 H, dd, *J* 7.7, 2.0 Hz, 8-H), 8.73 (1 H, s, 3-H);  $\delta_{\text{C}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) 102.55 (1-C), 117.53 (3-C), 123.35 (5-C), 124.01 (4a-C), 131.39 (6-C), 132.32 (7-C), 135.07 (8-C), 135.12 (8a-C), 147.21 (4-C), 151.91 (2-C).

### Naphthalene-1,3-diamine (**9**)

Compound **8** (1.05 g, 2.9 mmol) and tin(II) chloride dihydrate (9.84 g, 44 mmol) in ethyl acetate (100 mL) were heated under reflux for 17 h. The mixture was added to ice and sodium hydrogen carbonate was added until the aqueous layer was basic. The mixture was extracted with ethyl acetate and the combined extracts were washed with water and dried. Evaporation gave crude **9** as a dark brown solid:  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 3.71 (2 H, s, NH<sub>2</sub>), 4.08 (2 H, s, NH<sub>2</sub>), 6.23 (1 H, d, *J* 2.1 Hz, 2-H), 6.50 (1 H, d, *J* 1.9 Hz, 4-H), 7.18 (1 H, ddd, *J* 8.2, 6.8, 1.2 Hz, 7-H), 7.34 (1 H, ddd, *J* 8.0, 6.8, 1.0 Hz, 6-H), 7.53 (1 H, d, *J* 8.2 Hz, 5-H), 7.64 (1 H, d, *J* 8.4 Hz, 8-H);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 100.67 (4-C), 100.58 (2-C), 118.65 (8a-C), 120.67 (8-C), 121.36 (7-C), 126.39 and 126.42 (5-C and 6-C), 136.01 (4a-C), 143.28 (1-C), 144.71 (3-C).

### N,N'-Bis(*tert*-butoxycarbonyl)naphthalene-1,3-diamine (**10**)

The above crude **9** was heated under reflux with di-*tert*-butyl dicarbonate (3.11 g, 14.2 mmol) in tetrahydrofuran (30 mL) for 17 h. Evaporation and chromatography (dichloromethane) gave **10** (769 mg, 74%) as a pale buff solid: mp 127–130°C (lit.<sup>5</sup> mp 129–131°C);  $\nu_{\max}$  3254 (NH), 1716 (C=O), 1685 (C=O);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.54 (9 H, s, Bu<sup>t</sup>), 1.56 (9 H, s, Bu<sup>t</sup>), 6.63 (1 H, s, NH), 6.91 (1 H, s, NH), 7.34 (1 H, ddd, *J* = 8.1, 6.8, 1.3 Hz, 6-H), 7.44 (1 H, ddd, *J* 7.9, 6.9, 1.1 Hz, 7-H), 7.73 (1 H, d, *J* 8.2 Hz, 5-H), 7.77 (2 H, m, 1,8-H<sub>2</sub>), 7.93 (1 H, s, 3-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 28.37 (2 × CMe<sub>3</sub>), 80.63 (CMe<sub>3</sub>), 80.92 (CMe<sub>3</sub>), 110.65 (3,8-C<sub>2</sub>), 119.69 (5-C), 122.5 (4a-C), 124.41 (6-C), 126.49 (7-C), 128.52 (1-C), 133.76 (4-C), 134.82 (8a-C), 135.81 (2-C), 152.76 (C=O), 153.13 (C=O).

### N,N'-Bis(*tert*-butoxycarbonyl)-1-iodonaphthalene-2,4-diamine (**11**)

Compound **10** (417 mg, 1.28 mmol) was treated with N-iodosuccinimide (431 mg, 1.9 mmol) and 4-methylbenzenesulfonic acid hydrate (457 mg, 2.4 mmol) in tetrahydrofuran (7 mL) and methanol (7 mL) at -78°C. The mixture was allowed to warm slowly to 20°C over 4 h and was then diluted with aq. sodium thiosulfate (5%) and stirred at 20°C for 15 min. The mixture was extracted with ethyl acetate. The combined organic extracts were dried and the solvents were evaporated. Chromatography (dichloromethane) gave **11** (400 mg, 71%) as a pale buff solid: mp 166–168°C (lit.<sup>5</sup> mp 154–156°C);  $\nu_{\max}$  3384 (NH), 3229 (NH), 1733 (C=O), 1683 (C=O);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>)  $\delta$  1.55 (9 H, s, Bu<sup>t</sup>), 1.57 (9 H, s, Bu<sup>t</sup>), 6.86 (1 H, s, 4-NH), 7.17 (1 H, s, 2-NH), 7.43 (1 H, dd, *J* 8.0, 6.9 Hz, 6-H), 7.51 (1 H, dd, *J* 7.9, 1.1 Hz, 7-H), 7.76 (1 H, d, *J* 8.2 Hz, 5-H), 8.09 (1 H, d, *J* 8.4 Hz, 8-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 28.38 (2 × CMe<sub>3</sub>), 81.03 (CMe<sub>3</sub>), 81.28 (CMe<sub>3</sub>), 87.36 (1-C), 113.71 (3-C), 121.40 (5-C), 124.88 (4a-C), 125.32 (6-C), 128.15 (7-C),

132.58 (8-C), 134.65 (4-C or 8a-C), 134.82 (8a-C or 4-C), 138.22 (2-C), 152.68 (C=O), 153.21 (C=O).

### N-(1-Aminonaphthalen-3-yl)-2,2,2-trifluoroacetamide (**24**)

Naphthalene-1,3-diamine **9** (1.29 g, 8.16 mmol) was stirred in dry tetrahydrofuran (100 mL) under nitrogen at 0°C. N,N-Diisopropylethylamine (4.23 g, 32.6 mmol) was added, followed by dropwise addition of trifluoroacetic anhydride (1.71 g, 8.16 mmol) in dry tetrahydrofuran (100 mL) during 2 h. The mixture was allowed to warm slowly to 20°C during 16 h. The evaporation residue, in ethyl acetate, was washed with water and brine. Drying, evaporation and chromatography (petroleum ether / ethyl acetate 9:1 → 1:1) gave **24** (309 mg, 15%) as a buff solid: mp 168–169°C;  $\nu_{\max}$  3482, 3374, 3324 (NH), 1721, 1706 (C=O);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.99 (2 H, s, NH<sub>2</sub>), 7.01 (1 H, d, *J* 2.0 Hz, 2-H), 7.39 (1 H, ddd, *J* 8.2, 6.8, 1.3 Hz, 7-H), 7.47 (1 H, ddd, *J* 8.1, 6.8, 1.2 Hz, 6-H), 7.49 (1 H, d, *J* 1.4 Hz, 4-H), 7.75 (1 H, d, *J* 7.7 Hz, 5-H), 8.10 (1 H, d, *J* 8.4 Hz, 8-H), 11.17 (1 H, s, NH);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 101.31 (2-C), 106.51 (4-C), 115.88 (q, *J* 289.0 Hz, CF<sub>3</sub>), 120.89 (8a-C), 122.24 (8-C), 123.46 (7-C), 126.34 (6-C), 127.78 (5-C), 134.09 (4a-C), 134.67 (3-C), 145.56 (1-C), 154.41 (q, *J* 36.6 Hz, C=O);  $\delta_{\text{F}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) -73.69 (s, CF<sub>3</sub>); *m/z* (ES<sup>+</sup>) 277.0554 (M + Na) (C<sub>12</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>NaO requires 277.0565).

### *tert*-Butyl N-(3-trifluoroacetamidonaphthalen-1-yl)carbamate (**25**)

Compound **24** (330 mg, 1.30 mmol) was boiled under reflux with di-*tert*-butyl dicarbonate (1.43 g, 6.55 mmol) in dry tetrahydrofuran (10 mL) under N<sub>2</sub> for 16 h. Evaporation and chromatography (petroleum ether → petroleum ether / ethyl acetate 19:1) gave **25** (381 mg, 83%) as a pale buff solid. mp 206–208°C;  $\nu_{\max}$  3297 (NH), 3244 (NH), 1711 (C=O), 1683 (C=O);  $\delta_{\text{H}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) 1.57 (9 H, s, Bu<sup>t</sup>), 7.54 (1 H, td, *J* 8.2, 1.4 Hz, 7-H), 7.58 (1 H, td, *J* 8.0, 1.2 Hz, 6-H), 7.94 (1 H, d, *J* 8.1 Hz, 5-H), 8.00 (1 H, d, *J* 2.0 Hz, 2-H), 8.13 (1 H, d, *J* 8.2 Hz, 8-H), 8.20 (1 H, d, *J* 1.8 Hz, 4-H), 9.39 (1 H, s, *NHBoc*), 11.50 (1 H, s, *NHCOCF*<sub>3</sub>);  $\delta_{\text{C}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) 28.13 (CMe<sub>3</sub>), 79.26 (CMe<sub>3</sub>), 114.63 (2-C), 114.73 (4-C), 115.79 (q, *J* 288.8 Hz, CF<sub>3</sub>), 122.64 (8-C), 125.27 (8a-C), 125.33 (7-C), 126.75 (6-C), 128.03 (5-C), 133.52 (4a-C), 133.56 (3-C), 134.92 (1-C), 153.76 (Boc C=O), 154.68 (q, *J* 37.1 Hz, CF<sub>3</sub>C=O);  $\delta_{\text{F}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) -73.76 (s, CF<sub>3</sub>); *m/z* (ES<sup>+</sup>) 377.1120 (M + Na) (C<sub>17</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>3</sub> requires 377.1089).

### *tert*-Butyl N-(1-iodo-2-(trifluoroacetamido)naphthalen-4-yl)carbamate (**26**)

Compound **25** (336 mg, 0.95 mmol) in dry tetrahydrofuran (10 mL) was cooled to -78°C and stirred under N<sub>2</sub>. N-Iodosuccinimide (309 mg, 1.4 mmol) in dry tetrahydrofuran (2.0 mL) was added followed by 4-methylbenzenesulfonic acid hydrate (370 mg, 1.9 mmol) in dry tetrahydrofuran (2.0 mL). The temperature of the mixture was allowed to rise slowly to 20°C during 20 h. The reaction was quenched by addition of sat. aq. sodium hydrogen carbonate. The mixture was diluted with water and extracted with ethyl acetate. Drying, evaporation and chromatography (petroleum ether → petroleum ether / ethyl acetate 4:1) gave **26** (344

mg, 75%) as a pale buff solid: mp 198-199°C;  $v_{\max}$  3323, 3209 (NH), 1721 (C=O), 1698 (C=O);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>)  $\delta$  1.57 (9 H, s, Bu'), 6.95 (1 H, s, NHBoc), 7.54-7.61 (2 H, m, 6,7-H<sub>2</sub>), 7.82 (1 H, d,  $J$  8.1 Hz, 5-H), 8.14 (1 H, d,  $J$  8.6 Hz, 8-H), 8.58 (1 H, s, NHCOCF<sub>3</sub>), 8.71 (1 H, s, 3-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 28.31 (CMe<sub>3</sub>), 81.63 (CMe<sub>3</sub>), 89.87 (1-C), 113.26 (3-C), 115.77 (q,  $J$  289.3 Hz, CF<sub>3</sub>), 121.09 (8-C), 125.43 (8a-C), 126.86 (7-C), 128.73 (6-C), 133.17 (5-C), 134.52 (4a-C), 134.90 (4-C), 135.20 (2-C), 152.82 (Boc C=O), 155.05 (q,  $J$  38.0 Hz, CF<sub>3</sub>C=O);  $\delta_{\text{F}}$  ((CD<sub>3</sub>)<sub>2</sub>SO) -74.13 (s, CF<sub>3</sub>);  $m/z$  (ES<sup>+</sup>) 503.0100 (M + Na) (C<sub>17</sub>H<sub>16</sub>F<sub>3</sub>IN<sub>2</sub>NaO<sub>3</sub> requires 503.0055), 498.0542 (M + <sup>+</sup>NH<sub>4</sub>) (C<sub>17</sub>H<sub>20</sub>F<sub>3</sub>IN<sub>3</sub>O<sub>3</sub> requires 498.0500).

## Notes and references

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‡ NMR spectroscopic data for **16**. <sup>1</sup>H NMR (CDCl<sub>3</sub> / CF<sub>3</sub>CO<sub>2</sub>H, 293 K)  $\delta$  6.05 (1 H, s, 3-H), 6.51 (1 H, s, CHI), 7.58 (1 H, t,  $J$  = 7.8 Hz), 7.75 (1 H, d,  $J$  = 7.8 Hz), 7.70 (1 H, t,  $J$  = 7.8 Hz), 7.84 (1 H, d,  $J$  = 8.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub> / CF<sub>3</sub>CO<sub>2</sub>D, 293K)  $\delta$  9.79 (CHI), 91.49 (CH), 121.68 (C<sub>q</sub>), 124.16 (CH), 129.93 (CH), 131.48 (CH), 135.01 (CH), 141.25 (C<sub>q</sub>), 164.30 (CNH<sub>3</sub><sup>+</sup>), 173.50 (CNH<sub>3</sub><sup>-</sup>).

# To avoid confusion, all positions on the naphthalene ring are numbered in the discussion according to the iononaphthalene educts, with N-containing groups at 2- and 4-positions.

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